Validation of The Edinburgh Cognitive and Behavioural ALS Screen (ECAS) in behavioural variant Frontotemporal Dementia and Alzheimer's Diseas e

MÃ³nica Mariana De Icaza Valenzuela (Orcid ID: 0000-0002-9782-625X)

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Short running title: Validation of screen in bv FTD and AD

Authors:

Mónica M. De Icaza Valenzuela. 1, 2, 3

Dr Thomas H. Bak. 1, 2, 3

Dr Harriet E. Thompson. 1

Shuna Colville. 2, 3, 4

Dr Suvankar Pal. 2, 3, 4

Professor Sharon Abrahams. 1, 2, 3

Affiliations:

1. Human Cognitive Neuroscience –Psychology, School of Philosophy, Psychology and Language Sciences, University of Edinburgh

2. Anne Rowling Regenerative Neurology Clinic, University of Edinburgh

3. Euan MacDonald Centre for Motor Neurone Disease research, University of Edinburgh

4. Centre for Clinical Brain Sciences, University of Edinburgh

Corresponding author: Mónica M. De Icaza Valenzuela

Address: University of Edinburgh, 7 George Square, Edinburgh, EH8 9JZ, United Kingdom

Email address: s1365658@ed.ac.uk

Telephone: 07463 711002

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Declaration of interest

The authors have no known conflict of interest in relation to the publication of this paper.

Abstract

The Edinburgh Cognitive and Behavioural ALS Screen (ECAS) was developed to assess cognitive and behavioural changes in an anterior frontotemporal syndrome (executive functions, language, fluency and behaviour), common in Amyotrophic Lateral Sclerosis (ALS) and also assesses posterior cerebral dysfunction (memory and visuospatial abilities). **Objectives:** To validate the ECAS in behavioural variant Frontotemporal Dementia (bvFTD) without ALS, as compared with Alzheimer's Disease (AD), against comprehensive neuropsychological assessment. Compare its sensitivity to that of the Addenbrooke's Cognitive Examination (ACE-III) and investigate behavioural changes in both types of dementia.

Methods: Retrospective study of 16 people with bvFTD (without ALS), 32 with AD, and 48 healthy controls completed the ECAS, ACE-III and extensive neuropsychological assessment.

Results: The ECAS showed higher sensitivity (94%) and marginally lower specificity (96%) than the ACE-III for both the bvFTD and AD groups. The anterior composite subscore was sensitive for bvFTD (94%), and slightly less so for AD (84%), while the posterior composite subscore was sensitive for AD (97%), and less so for bvFTD (75%). All people with bvFTD that were impaired on the ECAS total and anterior composite scores were also impaired on the anterior function's tests of the neuropsychological assessment. A cut-off of 4 or more behavioural domains affected differentiated well between the bvFTD and AD groups, while a qualitative analysis of the behavioural interview found different themes between groups.

Conclusions: The ECAS is a valid and sensitive assessment for bvFTD without ALS and for AD. The carer behavioural interview makes it particularly suitable to detect behavioural abnormalities related to frontal lobe disorders.

Key words: ECAS, ACE-III, frontotemporal dementia, Alzheimer's disease, screen, cognition, behaviour, dementia, neuropsychology, qualitative

Key points:

1. The ECAS showed higher sensitivity (94%) and specificity (96%) for both the bvFTD and AD groups than the ACE-III.
2. The ECAS performed well against standard comprehensive neuropsychological assessment with perfect concordance between ECAS Total and Anterior functions composite scores, and performance on the anterior functions' tests of the neuropsychological assessment for the bvFTD group. The ECAS total and posterior

functions composite scores also showed good validity against the posterior functions' tests of the neuropsychology assessment for the AD group.

3. The most recurrent abnormal behaviour for the bvFTD group was loss of sympathy/empathy (100%), while the most recurrent theme for AD was loss of interest in normal activities (56%). Important thematic differences between diagnoses were (26%) lack of awareness and (66%) lack of manners in people with bvFTD, while AD patients (33%) had a loss of self-confidence.

Introduction

Amyotrophic Lateral Sclerosis (ALS) is the most common form of Motor Neurone Disease and has been typically characterised as a rapid neurodegenerative disease affecting movement (1). However, between 10-15% of people with ALS fulfil a diagnosis of frontotemporal dementia, most commonly the behavioural variant (bvFTD), and an additional 35% have milder and more specific cognitive impairment indicating a full spectrum of frontotemporal dysfunction (2,3). The Edinburgh Cognitive and Behavioural ALS Screen (ECAS) was developed to assess these cognitive and behaviour changes (4). It is designed to accommodate physical disability common in ALS, allowing for both written and spoken responses. As such, it is also well suited to assess cognitive functions in other diseases affecting motor functions, including Parkinson's Disease and Progressive Supranuclear Palsy (5).

The ECAS comprises a brief assessment of cognitive domains typically affected by anterior cerebral dysfunction: executive functions (including social cognition), language and verbal fluency, characteristically impaired in ALS. It also includes assessment of the domains which are typically affected by more posterior cerebral dysfunction: memory and

visuospatial abilities. These were included to differentiate between the frontotemporal syndrome in ALS, and cognitive deficits resulting from other disorders common in older adults, namely Alzheimer's Disease (AD) (6). Furthermore, the ECAS includes a behavioural interview with carers which assesses five domains based on the diagnostic criteria for bvFTD (7).

This brief assessment is sensitive in detecting mild cognitive impairment (without dementia) in ALS with impairments in executive, language and fluency (4). It has also been validated against comprehensive neuropsychological testing in ALS, showing good sensitivity and specificity (8,9) and convergent validity against other screening tests; the Montreal Cognitive Assessment (MoCA), Frontal Assessment Battery (FAB), Consortium to Establish a Registry for Alzheimer's Disease plus Scale (CERAD plus) and Addenbrooke's Cognitive Examination (ACE-III) (10-12). A recent study demonstrated that both bvFTD with and without ALS were impaired on the ECAS against a healthy control group (13). The study showed evidence of convergent validity with four standard neuropsychological tests of naming, spelling, cognitive inhibition (executive function) and social cognition. However, the study did not investigate the clinical utility of the test by validating performance against comprehensive clinical neuropsychology assessment or against more routinely used brief cognitive assessment/screening measures. The ACE-III is a commonly used cognitive screen, developed to assess different types of dementia; and was originally validated in both AD and FTD (14). However, its sensitivity in the detection of bvFTD has been inconsistent (15-18). Although the ACE-III includes an assessment of fluency (letters and animals), it lacks other tests of executive functions, impairment of which form part of the diagnostic criteria of bvFTD.

In the early stages of both bvFTD and AD, deterioration typically follows a region-specific

pattern with frontal lobe dysfunction beginning in the orbitofrontal cortex in bvFTD (19); and medial temporal and occipitoparietal regions in AD (20,21). Recent studies have revealed that the ECAS composite score, compromising memory and visuospatial performance, was as sensitive to AD as the ACE-III (22) and was effective at differentiating ALS from AD in a Greek population (6).

This study aimed to validate the ECAS and further determine its clinical utility in detecting the cognitive and behavioural impairments in bvFTD in comparison with AD. Specifically the aims were to:

1. Determine whether the cognitive section of the ECAS is successful in detecting bvFTD without ALS, as compared with AD and healthy controls, and in comparison, with the ACE-III. We hypothesize that the people with bvFTD would perform more poorly on the ECAS domains typically affected by anterior cerebral dysfunction (executive functions, fluency, language). In contrast people with AD would perform more poorly on those affected by more posterior cerebral dysfunction (memory and visuospatial).
2. Determine the validity of the ECAS total score, and composite scores against a comprehensive clinical neuropsychological assessment.
3. Investigate the utility of the behavioural interview and determine whether the themes reported differed between diagnostic groups.

Method

Participants

In this retrospective study we analysed data collected as part of routine clinical neuropsychological assessment from 16 people with bvFTD (9 males, mean age of 61 years

(±9.38, 38-72) and education of 12.56 years (±3.24, 10-20)), and 32 with AD (16 males, mean age of 61.18 years (±5.87, 49-71) and education of 12.13 years (±2.17, 10-18)) from the Edinburgh Cognitive Diagnosis Audit Research and Treatment Register (DART), hosted by the Anne Rowling Regenerative Neurology Clinic and the University of Edinburgh. For the quantitative analysis of the behavioural data, we analysed data from a subgroup of 15 people with bvFTD and 24 with AD. Qualitative data was retrospectively obtained from available hand written verbatim records of interviews with the carers/relatives of 15 people with bvFTD (10 males, mean age of 64.13 years (±8.80, 39-76) and education of 12.60 years (±2.99, 10-18)), and 25 people with AD (11 males, mean age of 62.80 years (±5.23, 53-71) and education of 12.04 years (±2.24, 10-18)), (13 and 23 of which were included in the quantitative analyses of the behavioural interview).

Diagnoses were supported by magnetic resonance imaging (MRI) brain and HMPAO-SPECT imaging findings; measures of cerebrospinal (CSF) total Tau, Phosphorylated Tau, and beta amyloid (Ab1-42); and/or disease-causing mutations identified following a neurodegenerative gene panel analysis. Diagnoses were made according to consensus criteria: Rascovsky et al. (7) for bvFTD and McKhann et al. (23) for AD.

Retrospective data of healthy participants (n=48, 29 males) was from a larger sample previously described by De Icaza Valenzuela et al. (12). Participants were selected to match the patient groups in age (60.06 years (±11.92, 38-78)) and education (13.66 years (±3.03, 9-19)). They were previously recruited from the local population and the Psychology Volunteer Panel of the University of Edinburgh. All were native English speakers without neurological illness or learning disabilities in their medical history.

Materials

Neuropsychological testing included the ECAS, both cognitive and behavioural sections (4) and the ACE-III (14). Impairments were determined using published abnormality cut-offs. The ECAS evaluates the domains of: memory, visuospatial, fluency, language and executive functions. In addition to the total score, the test also provides a composite score for more anterior cerebral functions (fluency, executive, and language, originally termed ALS-specific as these were the functions typically affected in ALS) and one for more posterior cerebral functions (memory and visuospatial, originally termed ALS non-specific). The ECAS also includes a short behavioural interview that is completed with a relative/carer of the patient. This interview includes 10 questions examining: disinhibition, apathy, loss of sympathy or empathy, perseveration, hyperorality or change in food preferences, and psychotic symptoms (4, see http://ecas.psy.ed.ac.uk). The carer is asked whether each behaviour occurs, to describe, and give examples of the behaviour.

Further extensive comprehensive neuropsychological assessment included a range of tests which are routinely clinically undertaken (Supplementary 1). Impairment for each test was determined according to their published cut-off scores for abnormality or based on the 5th percentile of published normative data. To determine the validity of the ECAS anterior and posterior functions composite scores against more extensive testing, the neuropsychological tests were grouped according to the cognitive domains which correspond with the ECAS (executive, language, fluency, memory, and visuospatial). Each domain was assessed by two or three neuropsychological tests, and an impairment in a domain was determined when performance on at least one of the tests was impaired. A deficit in anterior functions was classified when one of the following domains was impaired: fluency, language, and/or executive functions. A deficit in posterior functions was classified when either visuospatial and/or memory was impaired.

Ethical Approval

Patient data was collected from the Edinburgh Cognitive Diagnosis Audit Research and Treatment (DART) Register, South East Scotland A Research Ethics Committee approval 12/SS/0196, IRAS no 103819. The testing of healthy control participants was approved by The Psychology Research Ethics Committee of the University of Edinburgh.

Statistical Analysis

The data were analysed using SPSS statistics version 22. One-way between groups analysis of variance (ANOVA) were undertaken on parametric data to assess the difference between groups. Homogeneity of variance for all variables was unequal as determined by Levene's test, and we therefore used Welch's ANOVA with Games-Howell post hoc tests. ROC curves assessed the sensitivity and specificity of the ECAS and the ACE-III to detect diagnosis of bvFTD and probable AD against healthy controls.

Transcripts of the behavioural interviews were analysed thematically using the Framework Analysis Method (24), by two raters independently. The results of both analyses were subsequently discussed amongst the research group, and an agreement of the final themes was reached.

Results

Sensitivity of the ECAS in detecting bvFTD and AD as compared with the ACE-III

There was a significant difference between healthy controls and the two patient groups (bvFTD and AD) in the ECAS Total, composites and all domain scores, and in the ACE-III Total score,

but the two patient groups did not significantly differ in any of these scores (see Table 1). Fifteen of sixteen (94%) of the bvFTD group were impaired on the ECAS Total and the ECAS anterior functions composite score, while 12 (75%) were impaired on the posterior functions composite score. Fourteen of the bvFTD group also completed the ACE-III, of whom 11 (79%) scored within the abnormal range (82 or below) while a further patient scored within the borderline range (82-88). In the assessment of the AD group, 30/32 (94%) were impaired on the ECAS Total score, and 31 (97%) were impaired in the ECAS posterior functions composite score, while 27 (84%) were impaired on the anterior functions composite score. Twenty-five of the AD group completed the ACE-III, of which 23 (92%) scored below the cut-off of 88; and 20 (80%) scored below the cut-off of 82. The frequency of impairment on the ECAS was identical when using abnormality cut-offs adjusted for age and education (12).

The ECAS total cognitive score showed high and equal sensitivity and specificity (94%, 96% respectively) at detecting both bvFTD and AD using the established cut-off score of 105. In comparison, the ACE-III was less sensitive but had an equal specificity at detecting either diagnosis (bvFTD 79%,98%, AD 83%,98%) (see Table 2). The ECAS total score was the most sensitive measure in detecting bvFTD, followed closely by the ECAS anterior functions composite score (see Figure 1a). The ECAS posterior functions composite score was the most sensitive measure in detecting AD, followed by the ECAS total score (see Figure 1b). Although, both composite scores were sensitive to both diagnoses, there was no significant difference in any of the ECAS cognitive scores between patient groups. The anterior composite score of the ECAS had a sensitivity of 52% and a specificity of 43% to differentiate between the bvFTD and AD groups with a cut-off of 62. The posterior composite score of the ECAS had a sensitivity of 96% and a specificity of 36% to differentiate between the AD and bvFTD

groups with a cut-off of 23. The ECAS Total Score had a sensitivity of 76% and a specificity of 29% to differentiate between the AD and bvFTD groups with a cut-off of 91.

Power analyses were calculated in G*Power (25) for the comparison of means on the ECAS posterior functions. The current comparison of the bvFTD group with the healthy control group had a large effect size (d= 2.52) and a power of .99 when using an alpha of 0.05; however, the comparison of the bvFTD group and the AD group had a medium effect size (d= 0.55) and a much reduced power of .55 when using an alpha of 0.05. Therefore, power may have been an issue in detecting a difference between bvFTD and AD patients on the ECAS composite scores.

Validation of the ECAS against Comprehensive Neuropsychological Assessment

Thirteen of the bvFTD group also completed the comprehensive neuropsychological assessment. Twelve (92%) were impaired on at least one of the anterior cerebral function domains of the full assessment (Fluency and/or Language and/or Executive), and all of these were also impaired on the ECAS Total and ECAS anterior functions composite scores giving perfect concordance, with 100% sensitivity and specificity. The ACE-III had a good sensitivity (82%, specificity 100%) to the anterior cerebral function domains of the neuropsychological assessment. One person with bvFTD was impaired only on the posterior functions of the full neuropsychological assessment, and was not impaired on either brief assessment, although fell in the borderline range on the ECAS Total score (scored 108). Of note this person had five behavioural domain changes. The profile of impairment across the tests are summarised in Supplementary Table 2.

Two AD participants did not undertake the neuropsychological assessment, but all who did were impaired in the posterior functions of the neuropsychological assessment (Memory and/or

Visuospatial). However, the ACE-III did not detect five patients, the ECAS total score could not detect two patients, and the ECAS posterior composite score could not detect one patient who were impaired on the posterior functions of the full neuropsychological assessment. Therefore, the sensitivity of these brief assessments at detecting posterior cognitive dysfunction as determined by full neuropsychological assessment, was 93% ECAS Total score, 97% ECAS posterior score, and 79% ACE-III all with a specificity of 100%.

Behavioural Interview

The carers/relatives of 15 people with bvFTD and 24 people with AD completed the behavioural interview. The majority of the bvFTD group had behavioural changes in five domains, whereas the majority of the AD group had behavioural changes in two domains (see Figure 2). The most common behavioural changes were disinhibition, apathy and loss of empathy in bvFTD and apathy and perseverative behaviour in AD (see Supplementary Table 3). The total number of behavioural domains impaired differentiated between bvFTD and AD with a sensitivity of 79%, specificity 87% using a cut-off of 4 or more behavioural domains affected.

Thematic Analysis of Carer Behavioural Interview

Several themes distinguished the bvFTD from the AD patients (see Table 3). The themes below were present in bvFTD only.

- Immediacy/ Impatience (66%) – "If he wants to do something in the moment he does, regardless of the circumstances. He just cannot stop himself".
- Manners (66%) – "Puts his feet up on the chair in restaurants. He eats off other people's plates and licks the plates in public"
- Loss of initiation of actions (33%) – Needs prompting for daily tasks.

- Egocentrism (33%) – "Only displays interest if it is related to him or when he is the center of attention, if not he switches off completely"
- Binge eating (46%) – "Eats non-stop…loses control"
- Strange beliefs (20%) – "Won't wash the front of her head because of her diagnosis of FTD"
- Lack of awareness (26%) – Upset about restrictions in his driver's license. Becomes verbally aggressive if he feels relative is suggesting that he has dementia
- Not the same person (46%) – "Not my mum. Used to be incredibly polite and now quite rude"
- Accidental oversights or Mistakes (60%) – "Exploded flask because he put it directly on the hob"

The themes reported for AD only were:

- Eating less or lost weight (32%) – "Doesn't eat well or the full meal"
- Avoids cooking (24%) – "…scared to touch something hot"
- Stopped reading (24%)
- Misplacing items (8%) – "Teapot in the fridge"
- Difficulties solving problems (20%) – "Couldn't figure out how to plough a field he did every year"
- Lost confidence (33%) – "Apologizes a lot"

The most common themes in the people with bvFTD were: loss of sympathy/empathy (100%)- "Always used to be caring and giving, but not so much anymore", loss of interest in normal activities/hobbies (80%), reduced social interest, even with family and close friends (80%), simple repetitive movements (80%) (such as scratching and tapping), eating more

carbohydrates (80%), buying impulsively (73%)- "cannot pass a shop without buying things immediately", and compulsive behaviour (73%)- "Besotted with puzzles, does them obsessively". The most common themes in AD were: loss of interest in normal activities/hobbies (56%), impulsive decisions (33%), offensive/inappropriate jokes or comments (33%), and lost confidence (33%)- "apologizes a lot".

Discussion

The ECAS was successful in detecting the cognitive changes present in bvFTD and AD compared to healthy controls, although there were no significant group differences in scores between the two types of dementia. Using published abnormality cut-offs (4), the ECAS anterior functions composite score (sensitivity of 94% and a specificity of 92%) (which comprises the domains of Fluency, Executive Functions and Language) and the ECAS Total Score (sensitivity 94% and specificity 96%) were the most effective measures in our study at detecting bvFTD when compared to healthy controls. The percentage of impairment on the ECAS in the bvFTD group in our sample (94%) was similar to what has been previously reported (91%) (13). The posterior functions composite score (Memory and Visuospatial domains) (sensitivity 97% and specificity 96%) was the most effective measure at detecting AD when compared to healthy controls. Although the abnormality cut-off of 88 of the ACE-III had a slightly higher sensitivity (96%) than the ECAS Total Score (sensitivity 94% and specificity 96%), it had a much lower specificity (86%) at detecting AD. In contrast the abnormality cut-off of 82 of the ACE-III had a lower sensitivity although relatively equal specificity at detecting both bvFTD (79%, 98%) and

AD (85%, 98%).

The trade-off between sensitivity and specificity is important, particularly when deciding which cut-offs may be best suited for detecting a diagnosis or establishing cognitive impairments. Although both are multi-domain assessments, the ECAS and ACE-III are screening tests which should be used to indicate whether further neuropsychological investigation is warranted. In this situation, sensitivity is usually of more importance than specificity, as the screening test should capture all those cases who may have the disease/cognitive impairment. Nevertheless, it is important to balance between a small increase of sensitivity at the expense of a larger decrease in percentage of specificity (26). The higher cut-offs of both tests (110 for the ECAS and 88 for the ACE-III) were more sensitive to both diagnoses but with much lower specificity. Therefore, the ECAS Total Score with an abnormality cut-off of 105, showed high sensitivity without a large cost of specificity.

The ECAS also showed strong validity at detecting cognitive impairments as compared with the gold standard of neuropsychological assessment. There was a perfect concordance of the ECAS scores and impairment on the anterior functions tests of the neuropsychological battery for the bvFTD group with 100% sensitivity, and 100% specificity. The only bvFTD patient that was unimpaired on the ECAS was also not impaired in the anterior functions' tests of the neuropsychological battery but showed changes in the five behavioural domains of the ECAS. The presentation of behaviour change without cognitive impairment in FTD has been previously demonstrated (27). There was also good concordance between the deficits detected on the ECAS Total and posterior functions composite scores and impairments in posterior functions tests in the

comprehensive neuropsychological assessment for the AD group. The ECAS Total score failed to detect two AD patients, while the ECAS posterior functions composite score failed to detect one patient only and the ACE-III failed to detect five patients with cognitive impairments as determined by the neuropsychological assessment. The original ECAS validation study in people with ALS also involved a comparison against extensive neuropsychological assessment, but it was a prospective study where each cognitive domain was assessed by three standardised tests (8). Impairment in a domain of the neuropsychological assessment was defined when 2 out of 3 tests were impaired. The current study was retrospective and included data from routine clinical neuropsychological assessment, in which for some domains only two standardised tests were used. So as not to dismiss evidence of impairment and to be consistent across all our cognitive domains we defined impairment on a domain if one test was impaired only.

These findings indicate the possible utility of the ECAS in a broader clinical setting for the screening of the dementias. The ECAS has already been shown to be an effective cognitive screen for movement disorders of ALS (4), Parkinson's Disease, and Progressive Supranuclear Palsy (5). Since the total score of the ECAS was more sensitive to bvFTD and AD than the ACE-III; and it includes a behavioural interview, the ECAS could be used as an alternative for the ACE-III for a cognitive screen in the clinical setting. The ECAS also has the additional advantage of being less prone to ceiling effects and is less influenced by IQ than the ACE-III (12); and therefore, very useful for a young onset population in a dementia clinic.

In the quantitative analysis of the behavioural data, most bvFTD patients tended to have behavioural changes in the five domains, whereas AD patients had behavioural changes in

two domains. Although only three behavioural symptoms must be present to meet current diagnostic criteria for bvFTD (7), the cut-off of 4 or more behavioural domains affected had a higher sensitivity (79% sensitivity and 87% specificity) to differentiate between the diagnoses of bvFTD and AD in this study. The current diagnostic criteria may therefore not be as effective at differential diagnosis, particularly as some people with AD show behavioural changes as revealed here.

Apathy was one of the most prevalent behaviours in both patient groups (bvFTD 100%, AD 58%), which is consistent with the literature (28-30). Disinhibition was very prevalent in the bvFTD group (100%), and perseverative behaviour was the second most common behaviour in the AD group (45%, although it was also reported in 80% of bvFTD patients), which is congruent with the literature (31,32). Identifying apathy as a behavioural change in the screening process could help orientate the carers and clinicians to manage this symptom.

The qualitative thematic analysis of the behavioural interview uncovered a number of themes which differentiated between the two patient groups. Themes present in people with bvFTD only were centred around loss of control (immediacy, loss of manners, binge eating), changes in personality (egocentrism and not being the same person), loss of initiation actions, strange beliefs, anosognosia, and accidental oversights/mistakes. The most common theme in bvFTD patients was loss of sympathy/empathy, followed by compulsions; both of which have been reported previously (33-36). Of note both of these behaviours were also reported in ~a third of people with AD. Although changes in sympathy/empathy and compulsions may not help with differential diagnosis, they are still important for clinical management. The most common themes found in AD only were reduced eating and/or lost weight, avoids cooking, loss confidence and has stopped reading. Weight loss in Alzheimer's has been widely reported

(37,38). Avoidance of cooking observed in the AD group seem to emerge from fear of having an accident. Awareness of diagnosis in AD unlike the lack of awareness in people with bvFTD could play a role in whether people avoid certain activities and the loss in self-confidence. The types of behaviour change found in our study was in accord with the results of some previous studies; where bvFTD patients have been shown to have more compulsive behaviours, increased eating (specifically carbohydrates and binge eating), more selfishness with less social awareness, and a lack of insight regarding their own functional impairment when compared to AD patients (39-42). However, previous studies have used more quantitative questionnaires, where a behaviour is present or not; while in the current study, although this is used for the number of domains affected, the descriptions of behaviour change were further defined by exploring the interviews qualitatively through thematic analysis. The findings demonstrate that certain behaviours may help in differential diagnosis.

The overlap in cognitive presentations with memory and executive dysfunction between these two types of dementia can make differential diagnosis very difficult. The cognitive section of the ECAS has corresponding limitations and therefore although able to detect each diagnosis, cannot reliably differentiate between the two. However, the results of the ECAS behavioural screen proved effective in differentiating bvFTD from AD. It is noteworthy that the ECAS posterior composite score was sensitive to the bvFTD group, although less than the AD group, and 75% of the bvFTD group were impaired on this score. People with bvFTD can experience memory impairments, as the processes of encoding and retrieving often require executive functions for organizing the information (43). In parallel, the ECAS anterior composite score was also sensitive to AD, but less than the bvFTD group, and 84% were impaired on this measure. It is well recognized that people with AD may also experience executive dysfunction, and for example impairments have been repeatedly shown on tests

of divided attention (44). In addition, we have demonstrated that the between group comparison of the ECAS composite scores may have been under powered, particularly given the relatively small sample size of the bvFTD group. Nevertheless, despite this overlap in presentation, distinctive behavioural features were present which distinguished between the two groups. Of note, the ECAS behavioural screen was designed to detect behaviour changes which are typical of bvFTD, and was therefore closely based on the diagnostic criteria (7). It was also developed to provide a standardised method for measuring and assessing these changes. Given that the bvFTD group were diagnosed on the basis of this same criteria, it is inevitable that the screen would be sensitive to the types of behaviour change in this group."

We had expected to find a difference between the bvFTD and AD samples with the composite scores, as one study previously found the ECAS posterior score to be sensitive at differentiating between AD and ALS patients (6). However, ALS presents with a heterogenous spectrum of cognitive change, with at least 50% of patients typically cognitively intact. In line with this only 50% of their ALS patients were impaired on the ECAS Total score, whereas 94% of our bvFTD sample was impaired, indicating more severe and extensive impairment in the current patient group. Furthermore, the AD group from this previous study (6) were older than the current study (mean age of 67.19 vs 61.18 years old respectively), and it is possible that early onset AD (< 65 years of age) may have a slightly different cognitive profile from late onset (45,46). Nevertheless, a further study which compared the Greek version of the ECAS with the ACE-III (22) found similar results to those reported here; in which both composite scores were sensitive to AD, with the posterior composite score being the most sensitive measure. Strengths of this study were its thorough investigation of the clinical validity of the ECAS with these dementia groups and the inclusion of well characterised patients (diagnoses supported by

imaging, CSF, and/or genetic analysis). The validation against comprehensive neuropsychology reinforces the use of the ECAS as a useful screening tool for the cognitive assessment of patients with and without a motor disorder. Although some of the behavioural differences between bvFTD and AD have been investigated previously in other studies with quantitative questionnaires and semi structured interviews, this is the first study that analyses and compares the different themes reported on the ECAS behavioural screen in people with bvFTD and AD. The limitations of this study include the sample size, particularly for the bvFTD group, which resulted in a lack of power for the comparison between patient groups. Furthermore, the retrospective study design limited the analysis of the available neuropsychological test data.

The findings demonstrate that the ECAS could be used by clinicians to evaluate suspected frontal lobe disorders and AD. Using the ECAS as a first line screen for cognitive impairment where there is a suspicion of bvFTD could speed up the process of assessment, diagnosis and treatment for this disease. Behavioural interviews with the carers add to the utility of the cognitive screens and may bring to light possible changes which may be important for clinical management. The ECAS could also heighten awareness in carers of the possible behavioural changes the patients could experience, which may facilitate reporting to their health professional in the future (47).

Conclusions

The ECAS was successful in assessing the profile of cognitive and behavioural impairment in both bvFTD and AD. The combined score for memory and visuospatial assessment was particularly sensitive to AD, while the combined score for executive, fluency and language

functions was sensitive to bvFTD. The ECAS also shows strong validity against full neuropsychological assessment and was more successful than the ACE-III at detecting impairment in both bvFTD and AD. The inclusion of a behavioural interview in the ECAS makes it particularly suitable to aid in the diagnosis of behavioural abnormalities related to frontal lobe disorders, and can aid in distinguishing between bvFTD and AD.

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Tables and Figures

Table 1: Comparison of ECAS and ACE-III scores between bvFTD, AD, and control groups

	Welch's F	*p* value		Mean (SD) Range	*p* value patient group vs control	*p* value bvFTD vs AD
ECAS: bvFTD (n=16) AD (n=32) Controls (n=48)						
ECAS Total (max 136)	(2,29.47) = 89.63	<.001	bvFTD AD Controls	69.44 (±26.03) 20-108 71.84 (±21.58) 31-112 118.44 (±7.98) 102-134	<.001 <.001	=.946
Language (28)	(2,28.95) = 12.39	<.001	bvFTD AD Controls	22.50 (±5.06) 8-27 23.63 (±4.99) 8-28 27.02 (±1.49) 21-28	=.008 =.002	=.748
Fluency (24)	(2,31.41) = 40.36	<.001	bvFTD AD Controls	8.25 (±6.84) 0-20 12.00 (±6.44) 0-22 20.17 (±3.08) 10-24	<.001 <.001	=.180
Executive (48)	(2,29.51) = 52.11	<.001	bvFTD AD Controls	21.81 (±11.23) 2-37 22.97 (±11.12) 7-43 40.15 (±3.79) 32-47	<.001 <.001	=.939
Memory (24)	(2,33.37) = 159.72	<.001	bvFTD AD Controls	6.88 (±5.88) 0-17 4.28 (±4.51) 0-15 19.75 (±3.03) 12-24	<.001 <.001	=.287
Visuospatial (12)	(2,29.78) = 11.63	<.001	bvFTD AD Controls	10.00 (±2.28) 7-12 8.97 (±3.39) 1-12 11.56 (±0.94) 7-12	=.041 <.001	=.433
Composite score of Anterior functions (100)	(2,29.55) = 57.90	<.001	bvFTD AD Controls	52.56 (±20.05) 10-79 58.59 (±17.45) 28-90 87.13 (±6.42) 72-99	<.001 <.001	=.568
Composite score of Posterior functions (36)	(2,32.20) = 149.89	<.001	bvFTD AD Controls	16.88 (±7.39) 7-29 13.25 (±5.71) 3-25 31.31 (±3.30) 21-36	<.001 <.001	=.215
ACE-III: bvFTD (n=14) AD (n=25) Controls (n=44)						
ACE-III Total (100)	(2,23.68) = 39.84	<.001	bvFTD AD Controls	69.93 (±17.63) 22-90 69.92 (±15.24) 32-98 93.82 (± 4.26) 82-100	=.001 <.001	=1.000

behavioural variant Frontotemporal Dementia (bvFTD), Alzheimer's Disease (AD), Edinburgh Cognitive and Behavioural ALS Screen (ECAS), Addenbrooke's Cognitive Examination (ACE-III), Standard Deviation (SD)

Table 2: Sensitivity and specificity of the ACE-III and ECAS tests scores in detecting bvFTD and AD vs controls

		bvFTD		AD	
	Abnormality Cut-off	Sensitivity	Specificity	Sensitivity	Specificity
ACE-III Total	82	.786	.977	.833	.977
ACE-III Total	88	.857	.864	.958	.864
ECAS Total	105	.938	.958	.938	.958
ECAS Total	110	1.000	.812	.969	.812
Language	26	.750	.750	.656	.750
Fluency	14	.875	.937	.594	.937
Executive	33	.813	.958	.844	.958
Anterior Composite	77	.938	.917	.844	.917
Memory	13	.750	.958	.906	.958
Visuospatial	10	.438	.917	.531	.917
Posterior Composite	24	.750	.958	.969	.958

ECAS anterior composite (language, fluency, and executive) and ECAS posterior composite (memory and visuospatial), Abnormality cut-offs are both standard and borderline for both tests (Niven et al., 2015; Hsieh et al., 2013).

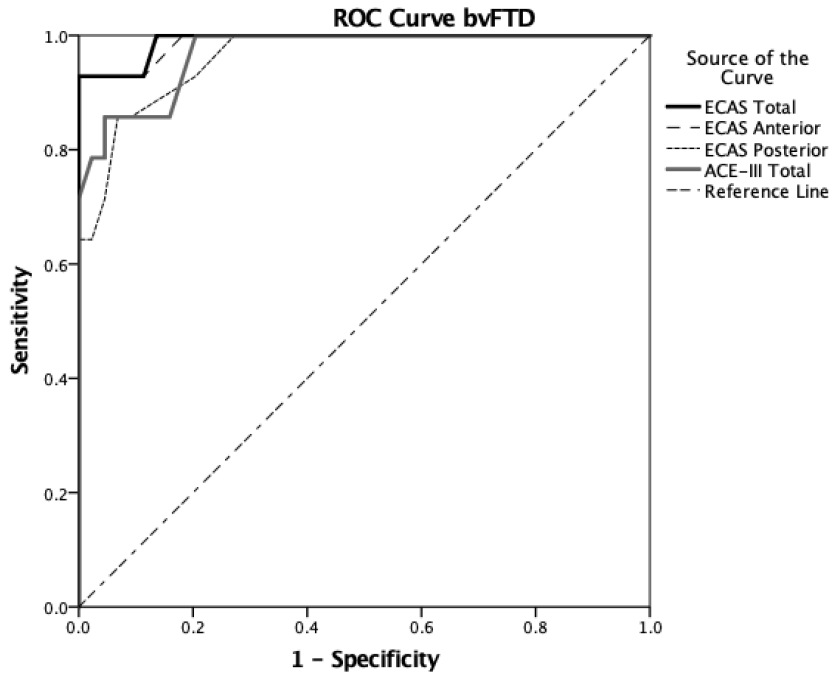
Table 3: Themes from the analysis of the behavioural interview
bvFTD (n=15) AD (n=25)

bvFTD %	Themes	AD %
	Impulsivity and Disinhibition	
73	Buying Impulsively	12
66	Immediacy/Impatience	
66	Loss of manners or decorum	
60	Impulsive Decisions	33
60	Offensive/Inappropriate jokes or comments	33
46	Aggression	8
33	Hypersexual behaviour	8
	Apathy	
80	Loss of interest in normal activities/hobbies	56
33	Emotional flatness	24
33	Loss of initiation actions	
20	Neglect of self-care	12
	Social interactions	
100	Loss of sympathy/Empathy	32
80	Reduced social interest	32
33	Egocentrism	
	Perseverative Behaviour	
80	Simple repetitive movements	24
73	Compulsive behaviour	32
40	Hoarding	20
26	Fixed Routine	12
	Eating and preparing food	
80	Eats more carbs	24
46	Binge eating	
	Eats less/lost weight	32
	Avoids cooking	24
	Psychosis	
46	Paranoia	24
20	hallucinations	12
20	Strange beliefs	
	Other	
60	Accidental oversights/Mistakes	
46	Disorientated	20
46	Not the same person/Change personality	
26	Lack of awareness/Anosognosia	
	Lost confidence	33
	Stopped reading	24
	Solving problems	20
	Misplace items	8

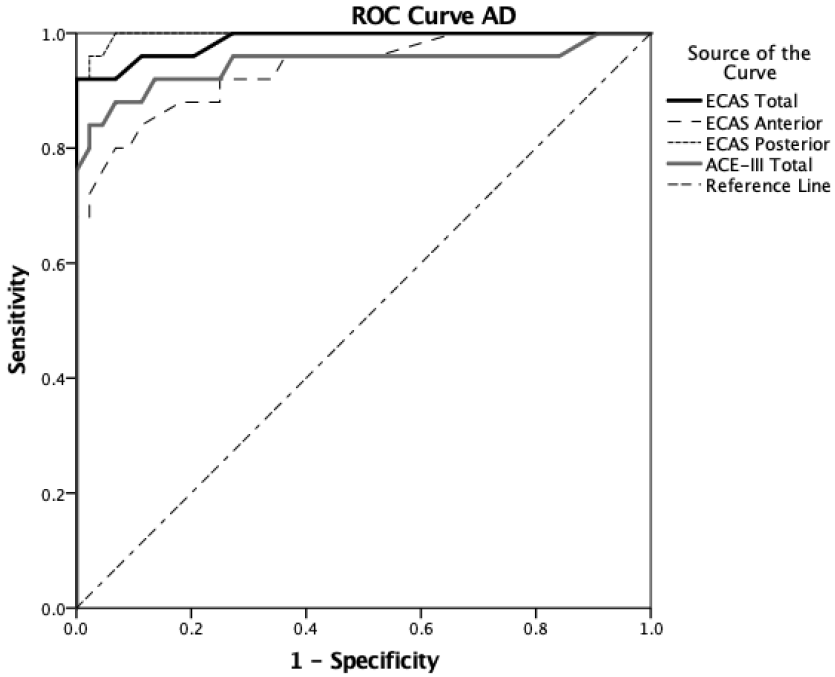
Alzheimer's Disease (AD), behavioural variant Frontotemporal Dementia (bvFTD)

Figure 1: Comparison of the ECAS and the ACE-III in detecting bvFTD (a) and AD (b) against controls.

(a)

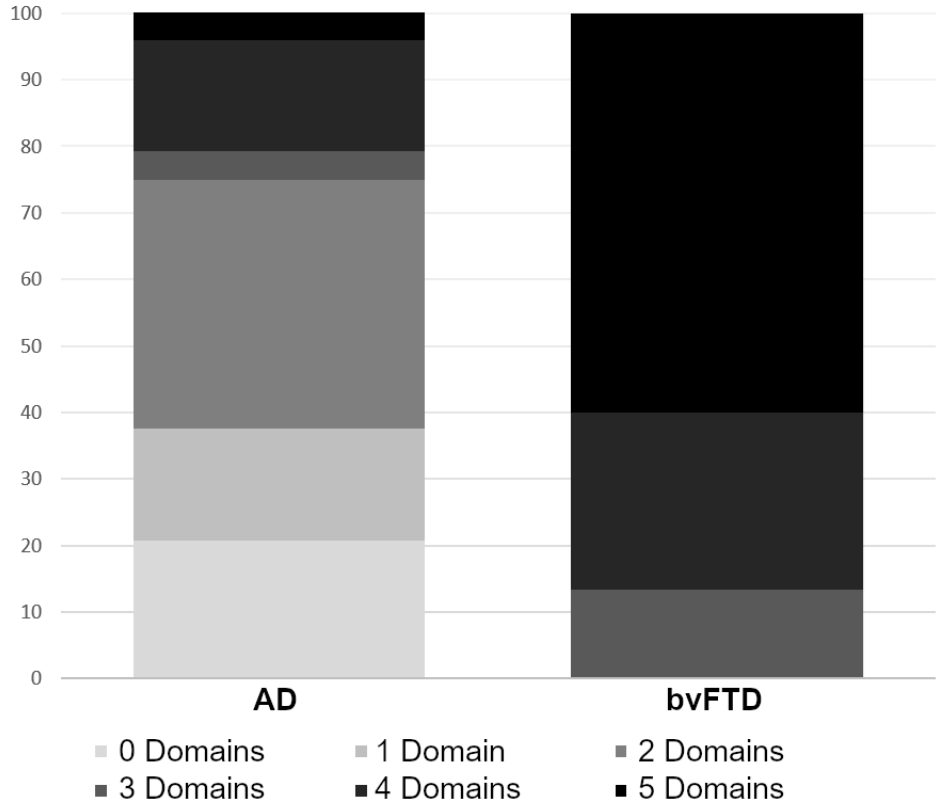


(b)



ECAS Anterior composite (language, fluency, and executive), ECAS Posterior composite (memory and visuospatial)

Figure 2: Percentage of the number of behavioural domains affected



Alzheimer's Disease (AD) n=24, behavioural variant Frontotemporal Dementia (bvFTD) n=15

Supplementary information for the article

Supplementary Table 1: Neuropsychological Tests

Cognitive Domain	Name of test	Reference
Cognitive Screen	Addenbrooke's Cognitive Examination (ACE-III)	Noone, 2015
Fluency	Controlled Oral Word Association (FAS)	Benton and Hamsher, 1983
	Category (Animal) Naming	Isaacs and Kennie, 1973
Language	The Graded Naming Test	Warrington, 1997
	Test of Reception of Grammar (TROG)	Bishop, 1989
Executive	Trail Making Test	Reitan and Wolfson, 1985
	The Sorting Test (The Delis-Kaplan Executive Function System)	Delis, Kaplan and Kramer, 2001
Memory	Free and Cued Selective Reminding Test (FSCRT)	Sarazin, et al., 2007
	BIRT Memory and Information Processing Battery Story and Figure Recall	Coughlan, Oddy and Crawford, 2007
Visuospatial	The Visual Object and Space Perception Battery	Warrington and James, 1991
	BIRT Memory and Information Processing Battery Figure copy	Coughlan, Oddy and Crawford, 2007

The tests are grouped into the cognitive domains which are assessed by the ECAS.

Supplementary Table 2: bvFTD and AD patients impairment on the ECAS, ACE-III and anterior and posterior functions neuropsychological tests

Number of patients	ACE-III	ECAS total	ECAS Anterior Composite Score	ECAS Posterior Composite Score	Neuropsychology Anterior Domains	Neuropsychology Posterior Domains
bvFTD						
6	X	X	X	X	X	X
2	X	X	X	✓	X	X
1	X	X	X	X	X	✓
2	✓	X	X	X	X	X
1	✓	✓	✓	✓	✓	X
1		X	X	X	X	X
1	X	X	X	X		
1	X	X	X	✓		
1		X	X	X		
AD						
15	X	X	X	X	X	X
3	✓	X	X	X	X	X
2	X	X	✓	X	X	X
1	X	✓	✓	✓	X	X
1	✓	X	✓	X	X	X
1	✓	✓	✓	X	X	X
1	X	X	X	X		X
5		X	X	X	X	X
1		X	X	X		X
1	X	X	X	X		
1		X	X	X		

Normal Range (✓), Impaired Range (X), Neuropsychology Anterior Domains: X is marked for impairment on language and/or fluency and/or executive functions in the comprehensive neuropsychological assessment. Neuropsychology Posterior Domains: X is marked for impairment on memory and/or visuospatial functions in the comprehensive neuropsychological assessment.

Supplementary Table 3: Behavioural Changes on the ECAS behaviour screen

AD (N=24) bvFTD (N=15)	AD	bvFTD
Disinhibition	33%	100%
Apathy and Inertia	58%	100%
Loss of Sympathy or Empathy	29%	87%
Perseverative	45%	80%
Hyperorality and Altered Food Preferences	25%	80%

Alzheimer's Disease (AD), behavioural variant Frontotemporal Dementia (bvFTD), Number of participants (n).